

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

WHAT IS CLAIMED IS:

1. A sustained release oral solid dosage form for absorption of a therapeutically active medicament in the gastrointestinal tract, comprising:

an effective amount of a medicament having a solubility of less than about 10 g/l to render a therapeutic effect;

a sustained release excipient comprising a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1; an inert pharmaceutical diluent selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, the ratio of said inert diluent to said gelling agent being from about 1:8 to about 8:1; and a pharmaceutically acceptable cationic cross-linking agent capable of crosslinking with said gelling agent and increasing the gel strength when the dosage form is exposed to an environmental fluid; the ratio of said medicament to said gelling agent being from about 1:3 to about 1:8, said dosage form providing a sustained release of said medicament when exposed to an environmental fluid.

2. The oral solid dosage form, of claim 1, wherein said heteropolysaccharide gum comprises xanthan gum and said homopolysaccharide gum comprises locust bean gum.

3. The oral solid dosage form of claim 2, wherein said cationic crosslinking agent comprises from about 0.5 to about 16 percent of said formulation, by weight.

4. The oral solid dosage form of claim 1, wherein said medicament has a solubility of less than about 1000 mg/l.

5. The oral solid dosage form of claim 4, wherein said medicament is a therapeutically effective dihydropyridine.

6. The oral solid dosage form of claim 1, wherein said medicament is selected from the group consisting of nifedipine, nimodipine, nivaldipine, nitrendipine, nisolidipine, niludipine, nicardipine and felodipine.

7. The oral solid dosage form of claim 1, wherein said cationic crosslinking agent comprises an alkali metal or an alkaline earth metal sulfate, chloride, borate, bromide, citrate, acetate, or lactate.

8. The oral solid dosage form of claim 1, wherein said cationic cross-linking agent comprises calcium sulfate.

9. The oral solid dosage form of claim 1, which further comprises an effective amount of a pharmaceutically acceptable wetting agent for said medicament.

10. The oral solid dosage form of claim 9, wherein said wetting agent is polyethylene glycol.

11. The oral solid dosage form of claim 1, wherein said gelling agent, said inert diluent, and said cationic cross-linking agent are granulated with a hydrophobic material selected from the group consisting of an alkylcellulose, a copolymer of acrylic and methacrylic acid esters, waxes, shellac, zein, hydrogenated vegetable oils, and mixtures of any of the foregoing, prior to incorporation of said medicament, said hydrophobic material being included in said dosage form in an amount effective to slow the hydration of said gelling agent when exposed to an environmental fluid.

12. The oral solid dosage form of claim 11, wherein said hydrophobic material is ethylcellulose.

13. The oral solid dosage form of claim 1 which is a tablet.

14. The oral solid dosage form of claim 1 which is in granular form.

15. The oral solid dosage form of claim 1, which comprises a gelatin capsule containing a sufficient amount of said granules to provide an effective dose of said therapeutically active medicament.

16. The oral solid dosage form of claim 1 which is a tablet, at least part of a surface of said tablet being coated with a hydrophobic material to a weight gain from about 1 to about 20 percent, by weight.

17. The oral solid dosage form of claim 9 which comprises a granulation which is coated with a hydrophobic material to a weight gain from about 1% to about 20%.

18. The oral solid dosage form of claim 17, wherein said hydrophobic material is selected from the group consisting of an alkylcellulose, a copolymer of acrylic and methacrylic and esters, waxes, shellac, zein, hydrogenated vegetable oils, and mixtures of any of the foregoing, prior to incorporation of said medicament, said hydrophobic polymer being included in said dosage form in an amount effective to slow the hydration of said gelling agent when exposed to an environmental fluid.

19. The oral solid dosage form of claim 11 which is a tablet, at least part of a surface of said tablet being coated with a hydrophobic material to a weight gain from about 1 to about 20 percent, by weight.

20. The oral solid dosage form of claim 19, wherein said mixture of sustained release excipient and medicament are coated with a hydrophobic material prior to tableting.

21. The oral solid dosage form of claim 1 which is a tablet, said tablet further comprising a coating containing from about 10 to about 40 percent of the total amount of said medicament included in said dosage form.

22. A method of preparing a oral extended release formulation of a medicament having poor solubility in water, comprising:

preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1, from about 1 to about 20 percent by weight of a cationic crosslinking agent capable of crosslinking with said gelling agent to increase the gel strength when exposed to an environmental fluid, and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent; and

adding an effective amount of a medicament having a solubility of less than about 10 g/l to render a desired therapeutic effect, such that a final product is obtained having a ratio of said medicament to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said formulation is exposed to environmental fluid and said formulation provides therapeutically effective blood levels of said medicament for at least 12 hours.

23. The method of claim 22, further comprising tableting said mixture of said sustained release excipient and said medicament.

24. The method of claim 23, further comprising coating said tablets with a hydrophobic coating to a weight gain from about 1% to about 20%.

25. The method of claim 22, further comprising granulating said sustained release excipient with a hydrophobic material.

26. The method of claim 22, wherein said medicament is nifedipine.

27. The method of claim 22, wherein said cationic cross-linking agent is calcium sulfate.

28. The method of claim 22, wherein said hydrophobic coating comprises ethylcellulose.

29. The method of claim 22, further comprising wetting said medicament with an effective amount of a pharmaceutically acceptable wetting agent prior to blending said medicament with said sustained release excipient.

30. The method of claim 29, wherein said wetting agent comprises polyethylene glycol.

31. The method of claim 29, further comprising coating said mixture of said sustained release excipient, said medicament and said wetting agent with a hydrophobic material.

32. The method of claim 22, wherein the amount of nifedipine is 20 mg, 30 mg, 60 mg or 90 mg.

33. The method of claim 22, wherein said sustained release excipient comprises from about 10 to about 75 percent gelling agent, from about 2 to about 15 percent cationic crosslinking agent, and from about 10 to about 75 percent inert diluent.

34. The method of claim 22, wherein said sustained release excipient comprises from about 30 to about 75 percent gelling agent, from about 5 to about 10 percent cationic crosslinking agent, and from about 15 to about 65 percent inert diluent.

35. The method of claim 22, wherein said formulation provides therapeutically effective blood levels of said medicament for at least 24 hours.

36. The method of claim 22, further comprising compressing the mixture of said sustained release excipient and said tablet into tablets.

37. A sustained release oral solid dosage form for providing an effective dose of nifedipine over a 24 hour period, comprising a sustained release excipient comprising from about 10 to about 99 percent by weight gelling agent comprising xanthan gum and locust bean gum in a ratio of about 3:1 to about 1:3; from about 0 to about 89 percent by weight of an inert pharmaceutically acceptable diluent selected from the group consisting of a monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, and from about 1 to about 20 by weight of a pharmaceutically acceptable cationic crosslinking agent capable of cross-linking with said gelling agent when exposed to an environmental fluid to increase the gel strength; and

from about 20 mg to about 90 mg of nifedipine; said gelling agent, said diluent and said cationic crosslinking agent being granulated with a hydrophobic material selected from the group consisting of an alkylcellulose, an copolymer of acrylic and methacrylic esters, waxes, shellac, zein, hydrogenated vegetable oils and mixtures of any of the foregoing, prior to the incorporation of said dose of nifedipine.

38. The dosage form of claim 37, further comprising a hydrophobic coating of from about 1 to about 20 percent of the total weight of said tablet, said coating covering at least a portion of the surface of said tablet.

39. The dosage form of claim 37, wherein said hydrophobic coating comprises a dispersion or solution of a plasticized hydrophobic polymer selected from the group consisting of an alkylcellulose, an copolymer of acrylic and methacrylic esters, and a mixture of the foregoing.

40. The dosage form of claim 37, wherein said gelling agent comprises from about 5% to about 65% of said tablet, by weight.

41. The dosage form of claim 37, wherein said cationic cross-linking agent comprises from about 1% to about 20% of said tablet, by weight.

42. The dosage form of claim 37, wherein said hydrophobic material comprises from about 0.5% to about 10% of said tablet, by weight.

43. The dosage form of claim 37, wherein said cationic cross-linking agent comprises calcium sulfate.

44. The dosage form of claim 37, wherein the amount of nifedipine is 20 mg, 30 mg, 60 mg or 90 mg.

45. The dosage form of claim 37, wherein said sustained release excipient comprises from about 10 to about 75 percent gelling agent, from about 2 to about 15 percent cationic cross-linking agent, and from about 30 to about 75 percent inert diluent.

46. The dosage form of claim 37, wherein said sustained release excipient comprises from about 30 to about 75 percent gelling agent, from about 5 to about 10 percent cationic cross-linking agent, and from about 15 to about 65 percent inert diluent.

47. The dosage form of claim 37, wherein said sustained release excipient further comprises from about 1% to 20% by weight of a hydrophobic material.

48. The dosage form of claim 47, wherein said nifedipine is mixed with an effective amount of a wetting agent, said mixture of said sustained release excipient and said medicament/wetting agent being coated with a hydrophobic material to a weight gain from about 1% to about 20%.

49. A sustained release oral solid dosage form for absorption of a therapeutically active medicament in the gastrointestinal tract, comprising:

an effective amount of a medicament having a solubility of less than about 10 g/l to render a therapeutic effect;

a sustained release excipient comprising a gelling agent, an inert pharmaceutical diluent selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, the ratio of said inert diluent to said gelling agent being from about 1:8 to about 8:1; and

an effective amount of a pharmaceutically acceptable cationic crosslinking agent capable of crosslinking with said gelling agent when exposed to an environmental fluid to increase the gel strength, the ratio of said medicament to said gelling agent being from about 1:3 to about 1:8, said dosage form providing a therapeutically effective blood levels of said medicament for at least about 12 hours.

50. The sustained release oral solid dosage form of claim 49, wherein said gelling agent, said diluent and said cationic crosslinking agent are granulated with a dispersion of a hydrophobic material selected from the group consisting of an alkylcellulose, a copolymer of acrylic and methacrylic esters, waxes, shellac, zein, hydrogenated vegetable oils, and mixtures of any of the foregoing prior to the incorporation of said medicament.

51. The sustained release oral solid dosage form of claim 49, wherein said hydrophobic material comprises from about 0.5% to about 10% of said sustained release excipient.

52. The sustained release oral solid dosage form of claim 49 which comprises a tablet, further comprising a tablet coating of hydrophobic material comprising from about 1% to about 20% of the total weight of said tablet, said tablet coating covering at least part of the surface of said tablet.

53. The tablet of claim 52, wherein said gelling agent comprises xanthan gum and locust bean gum in a ratio of about 3:1 to about 1:1.

54. The sustained release oral solid dosage form of claim 49, wherein said cationic crosslinking agent comprises from about 1% to about 20% by weight calcium sulfate.

55. A method of treating a patient with nifedipine, comprising,

preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent comprising xanthan gum and locust bean gum in a ratio of from about 1:3 to about 3:1, from about 1 to about 20 percent by weight of a cationic cross-linking agent, and from about 0 to about 89 percent by weight of an inert pharmaceutical filler;

adding an effective amount of nifedipine to render a desired therapeutic effect; -

tableting the resultant mixture such that a final product is obtained having a ratio of said medicament to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said tablet is exposed to gastrointestinal fluid and said tablet provides therapeutically effective blood levels of said medicament; and

administering said tablet to a patient at a predetermined dosage interval from about 12 to about 24 hours.

56. The method of claim 55, further comprising adding an effective amount of a wetting agent to said nifedipine to wet said nifedipine prior to mixing said nifedipine with said sustained release excipient, and coating said mixture of said wetted medicament and said sustained release excipient with a hydrophobic material prior to tableting in an amount effective to slow the initial dissolution of said medicament from said tablet when said tablet is exposed to gastrointestinal fluids.

57. The method of claim 56, further comprising coating said tablets with a hydrophobic material to a weight gain from about 1% to about 20%.

58. The method of claim 56, further comprising preparing said formulation such that it provides therapeutically effective blood levels of said medicament for at least 24 hours.

59. A sustained release oral solid dosage form for absorption of a therapeutically active medicament in the gastrointestinal tract, comprising:

an effective amount of a medicament having a solubility of less than about 10 g/l to render a therapeutic effect; and

a sustained release excipient comprising a gelling agent, an inert pharmaceutical diluent selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, the ratio of said inert diluent to said gelling agent being from about 1:8 to about 8:1, said gelling agent and said inert pharmaceutical diluent being granulated with a hydrophobic material selected from the group consisting of an alkyl-cellulose, a hydrophobic cellulosic material, a copolymer of acrylic and methacrylic acid esters, shellac, waxes, zein and mixtures of any of the foregoing, prior to the incorporation of said medicament, said hydrophobic material being included in an amount effective to slow the hydration of said gelling agent when said dosage form is exposed to an environmental fluid.

60. The sustained release oral solid dosage form of claim 59, wherein said gelling agent comprises xanthan gum and locust bean gum in a ratio from about 1:3 to about 3:1.

61. The sustained release oral solid dosage form of claim 59, wherein said hydrophobic material is included in an amount from about 1% to about 20% by weight of said sustained release excipient.

62. The sustained release oral solid dosage form of claim 59, wherein said hydrophobic material is included in an amount from about 1% to about 10% by weight of said dosage form.

63. The oral solid dosage form of claim 59, wherein said medicament is nifedipine.

64. The oral solid dosage form of claim 59, wherein the amount of nifedipine is 20 mg, 30 mg, 60 mg or 90 mg.

65. The oral solid dosage form of claim 59 which is a tablet, at least part of a surface of said tablet being coated with a hydrophobic material to a weight gain from about 1 to about 20 percent, by weight.

66. The oral solid dosage form of claim 59, wherein said granulate further comprises a coating of a hydrophobic material selected from the group consisting of an alkylcellulose, a copolymer of acrylic and methacrylic acid esters, waxes, shellac, zein, hydrogenated vegetable oils, and mixture of any of the foregoing.

67. A sustained release excipient, comprising:

a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum which crosslinks with said heteropolysaccharide gum when exposed to a fluid in an environment of use, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1;

an inert pharmaceutical diluent selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, the ratio of said inert diluent to said gelling agent being from about 1:8 to about 8:1; and

a pharmaceutically acceptable cationic cross-linking agent capable of crosslinking with said gelling agent when exposed to an environmental fluid.

68. The sustained release excipient of claim 67, wherein said heteropolysaccharide gum comprises xanthan gum and said homopolysaccharide gum comprises locust bean gum.

69. The sustained release excipient of claim 67, wherein said cationic crosslinking agent comprises from about 1 about 20 percent of said sustained release excipient, by weight.

70. The sustained release excipient of claim 67, wherein said gelling agent, said inert diluent, and said cationic cross-linking agent are granulated with a hydrophobic material selected from the group consisting of an alkylcellulose, a copolymer of acrylic and methacrylic acid esters, waxes, shellac, zein, hydrogenated vegetable oils, and mixtures of any of the foregoing, said hydrophobic material being included in an amount effective to slow the hydration of said gelling agent when exposed to an environmental fluid.

71. The sustained release excipient of claim 70, wherein said hydrophobic material is ethylcellulose.

72. A sustained release excipient comprising:

a sustained release excipient comprising from about 10 to about 99 percent by weight gelling agent, from about 0 to about 89 percent by weight of an inert pharmaceutically acceptable diluent selected from the group consisting of a monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, and from about 1 to about 20 by weight of a pharmaceutically acceptable cationic crosslinking agent capable of cross-linking with said gelling agent when exposed to an environmental fluid to increase the gel strength.

73. The sustained release excipient of claim 72, which comprises from about 10 to about 75 percent gelling agent, from about 2 to about 15 percent cationic crosslinking agent, and from about 30 to about 75 percent inert diluent.

74. The sustained release excipient of claim 72, which comprises from about 30 to about 75 percent gelling agent, from about 5 to about 10 percent cationic crosslinking agent, and from about 15 to about 65 percent inert diluent.

75. The sustained release excipient of claim 72, wherein said gelling agent comprises a heteropolysaccharide gum and a homopolysaccharide gum which crosslinks with said heteropolysaccharide gum when exposed to a fluid in an environment of use, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 3:1 to about 1:3.

76. The sustained release excipient of claim 75, wherein said heteropolysaccharide gum is xanthan gum and said homopolysaccharide gum is locust bean gum.

77. The sustained release excipient, comprising:

a gelling agent;

an inert pharmaceutical diluent selected from the group consisting of monosaccharide, a disaccharide, a polyhydric alcohol, and mixtures thereof, the ratio of said inert diluent to said gelling agent being from about 1:8 to about 8:1;

said gelling agent and said inert pharmaceutical diluent being granulated with a hydrophobic material selected from the group consisting of an alkylcellulose, a hydrophobic cellulosic material, a copolymer of acrylic and methacrylic acid esters, shellac, waxes, zein and mixtures of any of the foregoing, prior to the incorporation of said medicament, said hydrophobic polymer being included in an amount effective to slow the hydration of said gelling agent when said dosage form is exposed to a fluid in an environment of use.

78. The sustained release oral solid dosage form of claim 77, wherein said gelling agent comprises xanthan gum and locust bean gum in a ratio from about 1:3 to about 3:1.

79. The sustained release oral solid dosage form of claim 77, wherein said hydrophobic material is included in an amount from about 1 to about 20 percent, by weight.

80. The sustained release oral solid dosage form of claim 77, wherein said hydrophobic material is included in an amount from about 1 to about 10 percent, by weight.

81. A method for preparing a sustained release oral solid dosage form for a drug having a solubility of less than about 10 g/l, comprising

preparing a sustained release excipient comprising a gelling agent and a cationic crosslinking agent in an amount effective to crosslink said gelling agent when said gelling agent is exposed to fluid in an environment of use;

preparing a granulate of an effective amount of a medicament having a solubility of less than about 10 g/l with a pharmaceutically acceptable wetting agent, mixing said wetted medicament with said sustained release excipient;

coating said granulate with a hydrophobic material to a weight gain from about 1% to about 20%; and

preparing an oral solid dosage form suitable for human consumption by compressing an appropriate amount of said coated granulate into a tablet, or by incorporating an appropriate amount of said coated granulate into a gelatin capsule.